

### 3 RESULTS

The LD<sub>50</sub> values (24h) of dimethyl- and di-allyl-thiosulfinate were comparable, varying from 0.02 mg litre<sup>-1</sup> against *P. interpunctella* to 0.25 mg litre<sup>-1</sup> against *C. maculatus*, although those for thiosulfates were generally lower than those for disulfides.

In comparison, 24-h LD<sub>50</sub> values for some classical fumigants, tested in the same apparatus against three of the test species, were higher than those for the thiosulfinate compounds: they varied from 0.72 mg litre<sup>-1</sup> for dibromoethane/*C. maculatus* to 4.13 mg litre<sup>-1</sup> for dichloroethane/*S. oryzae* and were *c* 3–40 times higher than those for thiosulfates. In all cases, Lepidoptera were more sensitive to the compounds than Coleoptera.

### 4 CONCLUSION

In addition to the known nematicidal activity of thiosulfates,<sup>15</sup> the results indicate their potential in fumigation of stored products. They appear in fumigation of stored products. They appear to be possible substitutes for methyl bromide. These compounds need to be fully explored in terms of pungency and stability, as the lability of these active substances seem to exist only in the liquid state.<sup>16</sup>

### REFERENCES

- 1 Watson RT, Methyl bromide. Science and technology and economic synthesis report. *Fumigant and Pheromone* 29:1 (1992).
- 2 Anjana A, Sone LA and Gupta KC, Natural products as protectants of pulse beetles. *Bulletin of Grain Technology* 26:154–164 (1988).
- 3 Arnason JT, Philogene BJR and Morand P, *Insecticides of Plant Origin*. American Chemical Society Washington, DC (1989).
- 4 Grainge M and Ahmed S, *Handbook of Plants with Pest-Control Properties*. Wiley Interscience Publication, New York (1988).
- 5 Jacobson M, *Glossary of Plant-Derived Insect Deterrents*. CRC Press, Boca Raton, (1990).
- 6 Uvah III and Coaker TH, Effect of mixed cropping on some insect pests of carrots and onions. *Entomol Exp Appl* 36:159–167 (1984).
- 7 Potts MJ and Gunadi N, The influence of intercropping with *Allium* on some insect populations in potato (*Solanum tuberosum*). *Ann Appl Biol* 119:207–213 (1991).
- 8 Jones CG, Whitman DW, Compton SJ, Silk PJ and Blum MS, Reduction in diet breadth results in sequestration of plant chemicals and increases efficacy of chemical defense in a generalist grasshopper. *J. Chem Ecol* 15:1811–1812 (1989).
- 9 Nowbahari B and Thibout E, Defensive role of *Allium* sulfur compounds for leek moth *Acrolepiopsis assectella* Z. (Lepidoptera) against generalist predators. *J Chem Ecol* 18:1991–2002 (1992).
- 10 Auger J, Ferary S and Huignard J, A possible new class of natural sulfur pesticide for fumigation. *Ecologie* 25:27–35 (1994).
- 11 Ferary S and Auger J, What is the true odour of cut *Allium*? *J. Chromatography A*, 750:63–74 (1996).
- 12 Lecuyer P, Etude du pouvoir toxique des substances volatiles du poireau (*Allium porrum* L.) sur des insectes consommateurs ou non de cette plante. *Thèse 3<sup>e</sup> cycle*, Univ Tours (1975).

- 13 Nammour D, Auger J. and Huignard J, Mise en évidence de l'effet insecticide de composés soufrés (disulfures et trisulfures) sur *Bruchidius atrolineatus* (Pic) (Coléoptère: Bruchidae). *Insect Sci Applic* 10:49–54 (1989).
- 14 Auger J, Lecomte C and Thibout E, Leek odour analysis by gas chromatography and identification of the most active substance for the leek moth *Acrolepiopsis assectella*. *J Chem Ecol* 15:1847–1854 (1989).
- 15 Tada M, Hiroe Y, Kiyohara S and Suzuki S, Nematicidal and antimicrobial constituents from *Allium grayi* Regel and *Allium fistulosum* L. var. *caespitosum*. *Agric Biol Chem* 52:2383–2385 (1988).
- 16 Auger J, Lalau-Keraly FX and Belinsky C, Thiosulfates in vapor phase are stable and they can persist in the environment of *Allium*. *Chemosphere* 21:837–843 (1990).

### Synthesis and insecticidal activity of nitroguanidine derivatives

Hideki Uneme,\* Koichi Iwanaga, Noriko Higuchi, Yasuyuki Kando, Tetsuo Okauchi, Atsuo Akayama and Isao Minamida

Agricultural Research Laboratories, Agro Company, Takeda Chemical Industries, Ltd, 10 Wadai, Tsukuba, Ibaraki 300-4293, Japan

**Abstract:** Nitroguanidine derivatives with thiazol-5-ylmethyl moieties were prepared and their insecticidal activities against homopterous pests were tested. New synthetic routes for 2-chloro-5-chloromethylthiazole from 2,3-dichloro-1-propene and for substituted nitroguanidines from *S*-methyl-*N*-nitroisothiourea were established. Biological evaluation led to a novel insecticide (*E*)-1-(2-chlorothiazol-5-ylmethyl)-3-methyl-2-nitroguanidine (TI-435) which has a broad activity spectrum and is under development.

**Keywords:** neonicotinoid; nitroguanidine; insecticidal activity; structure–activity relationship; TI-435

### 1 INTRODUCTION

So-called neonicotinoids are establishing themselves as a new class of insecticide.<sup>1,2</sup> The first successful member of this family was imidacloprid,<sup>3</sup> developed by Nihon Bayer Agrochem KK, Japan. Takeda Chemical Industries, Ltd has already commercialised the acyclic neonicotinoid, nitenpyram,<sup>4</sup> which is highly active against homopterous and thysanopterous pests.

This summary describes a continuation of the study on neonicotinoids which showed that acyclic nitroguanidine analogs with a thiazol-5-ylmethyl group have also good activity (Fig. 1).

### 2 METHODS

#### 2.1 Synthesis

The synthetic routes for the thiazol-5-ylmethyl moieties are described in Fig. 2. 2-Amino-5-methyl-

\* Correspondence to: Hideki Uneme, Agricultural Research Laboratories, Takeda Chemical Industries Ltd, 10 Wadai, Tsukuba, Ibaraki 300-4293, Japan.  
E-mail: uneme-hideki@takeda.co.jp  
(Received 23 June 1998; accepted 30 September 1998)

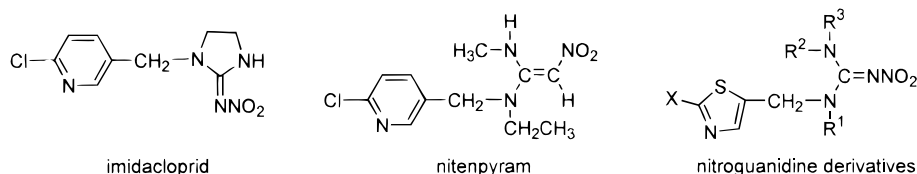


Figure 1. Neonicotinoid insecticides.

thiazole was subjected to Sandmeyer reaction to give 2-halo analogs,<sup>5,6</sup> which were converted into 5-halomethyl derivatives **1a** and **1b** by side-chain halogenation. Since 2-chloro-5-chloromethylthiazole (**1a**) became an important intermediate as the result of the biological evaluation, we looked for a more convenient method for preparing this compound and found that the reaction of 2-chloro-2-propenyl isothiocyanate, obtained from 2,3-dichloro-1-propene and potassium thiocyanate with chlorine or sulfur chloride, gave **1a** in an excellent yield.<sup>7</sup> Where X is hydrogen, methyl, trifluoromethyl or phenyl, 5-halomethyl compounds **1c–1f** were prepared according to known and similar methods<sup>8</sup> via ethyl 5-thiazolecarboxylates. The halomethyl compounds **1a–1f** were then converted into 5-amino-methylthiazoles **2** by conventional aminations. The 2-methylthio congener **2b** was obtained from 2-chloro compound **2a** and sodium methanethiolate.

When we started this work, no routes were available to prepare the nitroguanidine moiety satisfactorily. Although we had already synthesised several compounds, with some difficulties,<sup>9</sup> research resulted in the discovery of a novel method<sup>10</sup> which is widely applicable and which produces the desired compound in excellent yield. The new route is illustrated in Fig. 3. *S*-Methyl-*N*-nitroisothiourea,<sup>11</sup> which is readily available, was converted into *N*-phthaloylisothiourea **3** as a key intermediate by reaction with phthaloyl chloride. The reaction of **3** with 5-aminomethylthiazoles **2** gave *N*-thiazolyl-

methylisothioureas **4** in good yields with the elimination of phthalimide. The isothioureas **4** were treated with amines, affording nitroguanidine derivatives **5**. To prepare final compounds with an acyl substituent at R<sup>1</sup>, isothiourea **4a** was acylated before the reaction with amines. Nitroguanidines **5** with acyl substituents at R<sup>3</sup> were synthesised by the reverse introduction of the two amino segments. Thus, **3** was treated first with alkyl amines to give isothioureas **6**. After acylation of **6**, the resulting compounds **7** were reacted with **2** to obtain the desired products **5** in good yields.

## 2.2 Insecticidal activity

The order of the insecticidal potency in Fig. 4 was determined based on the data averaged over those for the three homopterous species *Nilaparvata lugens* Stal, *Aphis gossypii* Glov. and *Myzus persicae* Sulz by foliar application.

## 3 RESULTS

The structure activity relationships found with these compounds are shown in Fig. 4. At the substituent X, the compounds with a halogen atom (chlorine and bromine) showed most potent activity; that of the compounds with trifluoromethyl, hydrogen and methyl was intermediate and that with methylthio and phenyl was inferior to the others. For R<sup>1</sup>, unsubstituted compounds were active, and the introduction of an acyl group was also effective. Substitution with alkyl groups did not result in significant

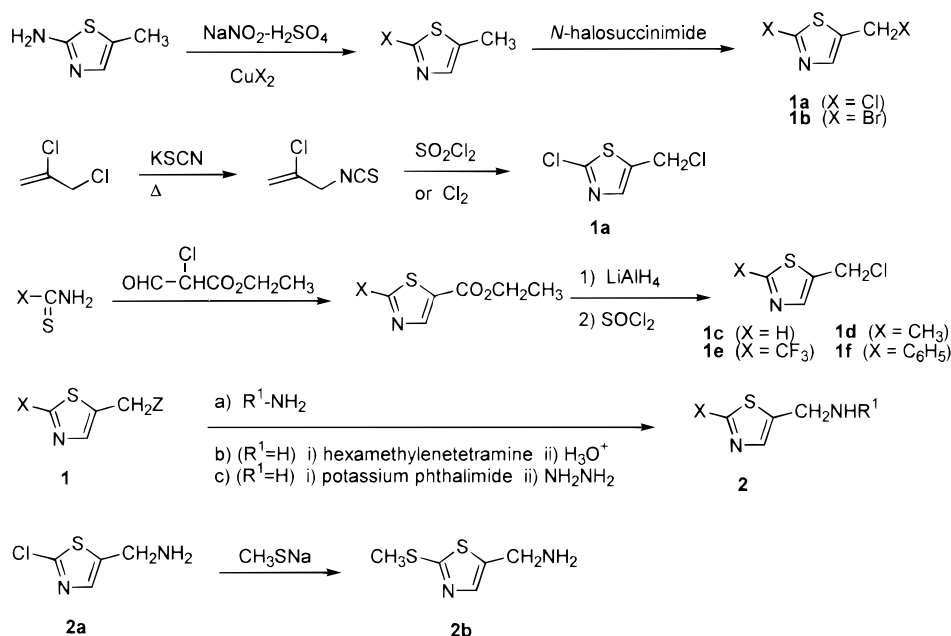


Figure 2. Synthetic routes for the thiazol-5-ylmethyl moieties.

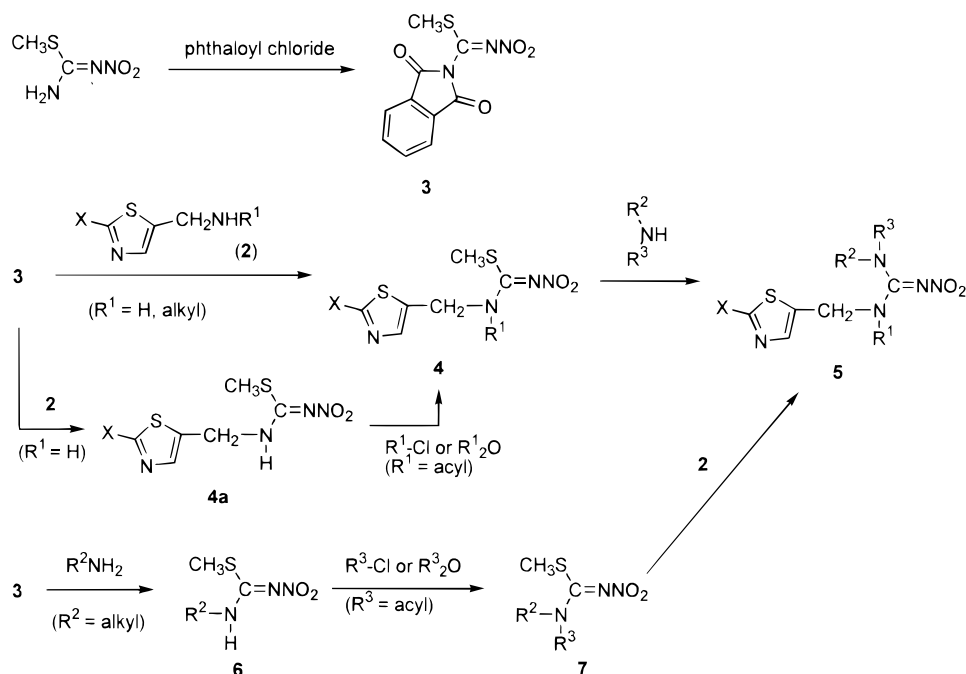


Figure 3. Novel method for nitroguanidine derivatives.

activity. At  $R^2$ , substitution by a methyl group achieved the greatest activity, but this decreased when ethyl, hydrogen and acetyl were employed at this position. Results of substitution at  $R^3$  were

similar to those for  $R^1$  substitution except that introduction of a methyl group improved activity. In total, the optimal activity was observed when X was a chlorine atom,  $R^1$  and  $R^3$  were hydrogen

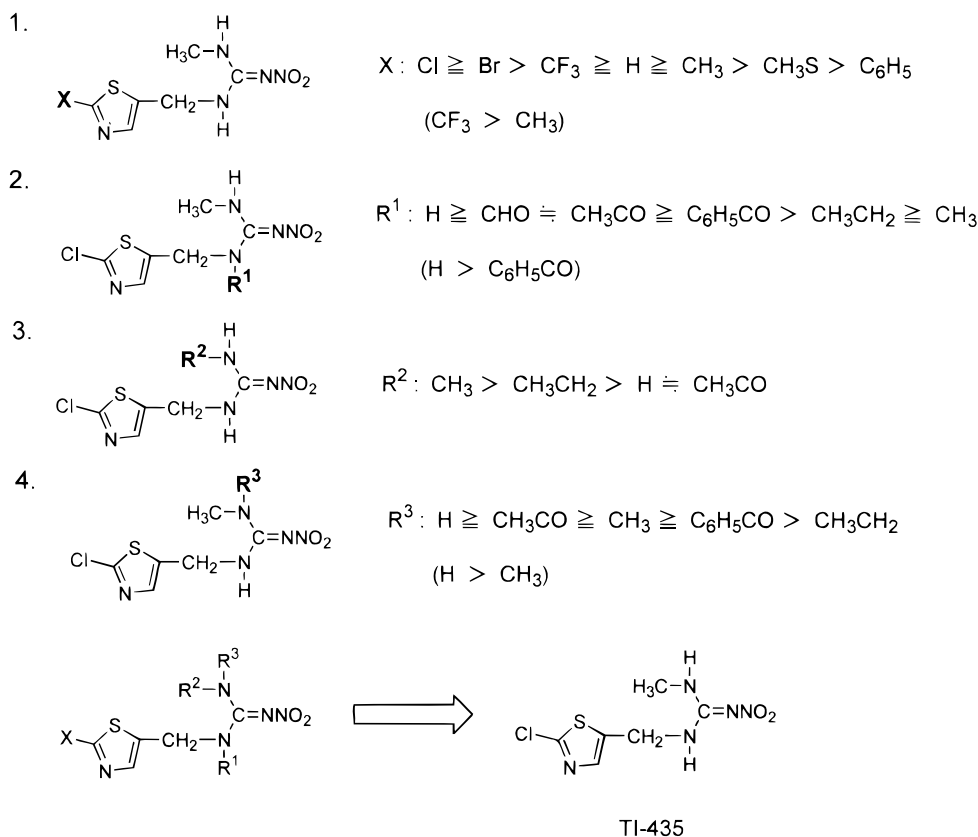


Figure 4. Results of structure-activity relationships.

atoms, and R<sup>2</sup> was a methyl group. The selected compound (*E*)-1-(2-chlorothiazol-5-ylmethyl)-3-methyl-2-nitroguanidine (code No TI-435) is now under development. TI-435 provides prominent control not only of homopterous pests but also of heteropterous, coleopterous, dipterous, thysanopterous and lepidopterous pests by foliar application, soil and treatment and seed treatment at low use rates.

## REFERENCES

- 1 Yamamoto I, Nicotine to nicotinoid *Abstr Pap Am Chem Soc* 214 Meet AGRO001 (1997). See also other abstracts: *ibid* AGRO002-006 and 017-024.
- 2 Kagabu S, Studies on the synthesis and insecticidal activity of neonicotinoid compounds *Nihon Noyaku Gakkaishi (J Pestic Sci)* 21:231-239 (1996).
- 3 Shiokawa K, Tsuboi S, Iwaya K and Moriya K, Development of a chloronicotinyl insecticide, imidacloprid. *Nihon Noyaku Gakkaishi (J Pestic Sci)* 19:329-332 (1994).
- 4 Minamida I, Iwanaga K, Tabuchi T, Aoki I, Fusaka T, Ishizuka H and Okauchi T, Synthesis and insecticidal activity of acyclic nitroethene compounds containing a hetero-arylmethylamino group *Nihon Noyaku Gakkaishi (J Pestic Sci)* 18:41-48 (1993).
- 5 McLean J and Muir GD, Reactions of certain thiazoles and glyoxalines with picryl chloride and 2,4-dinitrochlorobenzene. *J Chem Soc*:383-386 (1942).
- 6 Ganapathi K and Venkataraman A, Chemistry of the thiazoles Part III. Synthesis of thiazole derivatives unsubstituted in position 2: an evaluation of various possible methods. *Proc Indian Acad Sci* 22A: 362-378 (1945).
- 7 Uneme H, Higuchi N and Minamida I, Process for the preparation of chlorothiazole derivatives, *EP Patent* 446913, 1991.
- 8 Mashraqui SH and Keehn PM, Cyclophanes. 14. Synthesis, structure assignment and conformational properties of [2.2](2,5)oxazolo- and thiazolophanes. *J Am Chem Soc* 104:4461-4465 (1982).
- 9 Uneme H, Iwanaga K, Higuchi N, Minamida I and Okauchi T, Guanidine derivatives, their production and insecticides. *EP Patent* 376279, 1990.
- 10 Kando Y, Uneme H and Minamida I, Novel intermediates for preparing guanidine derivatives, their preparation and use. *EP Patent* 452782, 1991.
- 11 Fishbein I and Gallagher JA, The preparation and reactions of 2-alkyl-1(or 3)-nitro-2-thiopseudourea. Part I. Reaction with amines. *J Am Chem Soc* 76:1877-1879 (1954).

## Insect-neuroactive substances in two species of the genus *Liquidamber*

S Nakajima,\* T Takeda, K Nakahira, T Nitoda and N Baba

Department of Bioresources Chemistry, Faculty of Agriculture, Okayama University, Okayama 700, Japan

**Abstract:** Three insect-neuroactive substances from *Liquidamber styraciflua* and *L. formosana* were iso-

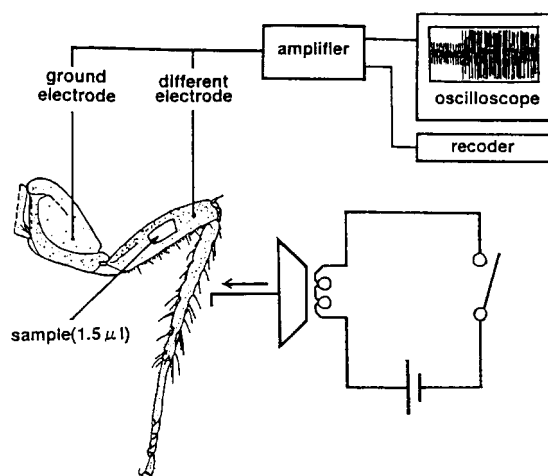
lated and characterized by spectral analyses as betulonic acid, 1-methoxy-9-caryolanol and eudesm-4(14)-ene-1,6-diol, respectively.

**Keywords:** Insect-neuroactive substances; betulonic acid; 1-methoxy-9-caryolanol; eudesm-4(14)-ene-1,6-diol; *Liquidamber styraciflua*; *Liquidamber formosana*

The plant kingdom offers numerous groups of compounds which exhibit a variety of biological activities. The diversity of complex chemical structures of such natural products is a valuable source of leads from which novel synthetic compounds can be developed. We can detect such products through screening the extracts from plants by suitable bioassays. A wide range of synthetic and natural chemicals have been shown to exert specific actions on insect tissues or nerves, and advances in methods for recording the electrical properties of insect nerves have been valuable in determining the molecular mechanisms of novel neuroactive agents including insecticides.<sup>1</sup>

During the course of studies on natural insect-neuroactive substances in plants, we have established a simple and sensitive bioassay for screening compounds, the layout of which is shown in Fig 1.<sup>2</sup> This shows the preparation of the metathoracic leg nerve of American cockroach, *Periplaneta americana* L., which involves insertion of pin electrodes into a cockroach leg. The metathoracic leg of an adult male cockroach was cut off and the cuticle removed for administration of the sample solution; the sensilla trichodia was fitted with a wire which was connected to a small speaker. The input to stimulate the motor nerve in the leg was measured as the concentration needed to stimulate the frequency of spontaneous discharges of the leg nerve cord.

Using this bioassay, the methanol extracts of various plants, including about 40 Kenyan and 15



**Figure 1.** Bioassay method for measuring the electrical responses from the metathoracic leg nerve of *Periplaneta americana*.

\* Correspondence to: S Nakajima, Department of Bioresources Chemistry, Faculty of Agriculture, Okayama University, Okayama 700, Japan.

(Received 29 June 1998; accepted 30 September 1998)